REMARKS

Upon entry of the presently made amendments, claims 1-19 will be pending. Claims 20-28 have been canceled without prejudice for being drawn to non-elected groups.

Claims 1, 9 and 16 have been amended to recite that the disease to be treated or prevented is associated with a nonsense mutation. Support for these amendments is found in the specification as filed at least at page 6, lines 27-29 and page 7, lines 26-28.

Claim 19 has been amended to recite that the cancer cell has a nonsense mutation. Support for this amendment is found in the specification as filed at least at page 7, lines 3-8.

No new matter has been added.

Applicants reserve their right to prosecute the subject matter of any canceled or amended claim or any unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

I. The Rejection of Claims 1-19 Under 35 U.S.C. § 112, First Paragraph

Claims 1-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse this rejection.

While acknowledging that the specification is enabling for the treatment of specific p53-associated tumors, the Examiner has stated that the specification does not reasonably provide enablement for the treatment of every type of cancer in existence.

Preliminarily, Applicants note that the amended method of use claims are directed to treating or preventing diseases associated with a nonsense mutation and to inhibiting the growth of a cancer cell having a nonsense mutation in its DNA or RNA. Accordingly, the amended claims are not directed to the treatment or prevention of every cancer or inhibiting the growth of every type of cancer cell.

Applicants have discovered that compounds of the present method of use claims have activity as nonsense mutation suppressors, meaning that they allow the translation of mRNA to continue past a nonsense mutation resulting in the production of full length protein. It is known that numerous diseases are caused in whole or in part by a lack of full length protein due to a nonsense mutation. Thus, compounds of the present method of use claims which have activity as nonsense mutation suppressors are useful for treating and preventing diseases caused by a nonsense mutation.

Applicants respectfully point the Examiner to the decision in *In re Bundy* wherein the United States Court of Customs and Patent Appeals held that all that is necessary to satisfy the how-to-use (*i.e.*, enablement) requirement of 35 U.S.C. § 112 is the disclosure of some

activity coupled with the knowledge as to the use of this activity. *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981). Accordingly, Applicants respectfully submit that the amended claims are enabled because the specification demonstrates the biological activity (*i.e.*, nonsense mutation suppression) of compounds of the method of use claims and provides a nexus between nonsense mutations and the claimed diseases. Nevertheless, the Examiner's discussion of the factors set forth in *In re Wands*, 8 U.S.P.Q. 1400 (C.A.F.C. 1988) is addressed below. Applicants note that the Examiner appears to have examined the "treating" and "preventing" aspects of the claims separately. Accordingly, Applicants address the "treating" aspect of the claims in the present section and the "preventing" aspect of the claims in Section II, below.

Nature of the Invention

The Examiner stated that the invention is *inter alia* a method for treating cancer. Applicants respectfully submit that the pending claims recite methods for treating cancer associated with a nonsense mutation and are not directed to the treatment of every cancer.

The State of the Prior Art

The Examiner stated that the skilled artisan would view cancer as a group of maladies not treatable by a single medicament, that no one drug is useful for the treatment of every case of cancer, and that certain cancers either do not respond well to any known drug or respond only to certain drugs. Applicants note that the amended claims are not directed to the treatment of every cancer, but rather are directed to the treatment of diseases, including cancer, associated with a nonsense mutation. Applicants respectfully submit that the state of the art is high with respect to the treatment of disease associated with nonsense mutations in that the nexus between nonsense mutations and certain diseases is well known.

The Relative Skill of Those in the Art

Applicants agree with the Examiner's acknowledgment that the level of skill in the art is high.

The Predictability or Unpredictability of the Art

The Examiner stated that no single treatment is effective for all cancers, that one skilled in the art would recognize that the treatment of cancer is highly unpredictable and that the mechanism disclosed by the specification is not applicable to all cancers.

Applicants respectfully submit that although the treatment of cancer, like many diseases, is not absolutely predictable, cancer can and has been treated. Indeed, the Federal

Circuit has specifically stated that the treatment of cancer with chemical compounds does not suggest an unbelievable undertaking or involve implausible scientific principles. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). Furthermore, Applicants respectfully submit that the amended claims are directed to the treatment of diseases, including cancer, associated with a nonsense mutation, so the mechanism disclosed by the specification is, in fact, applicable to all claimed diseases, including cancer.

The Examiner further stated that Zambetti *et al.* (cited in Applicant's Form PTO-1449 as reference C24) discloses that a mutant p53 gene may cause cancer through a gain-of function mutation and that overcoming oncogenesis by this mechanism would require suppression of the mutant p53. Applicants respectfully submit that the claims are directed to diseases, including cancer, associated with a nonsense mutation and, accordingly, are not directed to the treatment of cancers caused by a missense, gain of function or frameshift mutation which would result in the expression of mutant p53 as described in Zambetti *et al.*

The Breadth of the Claims

The Examiner stated that claims 1-13 are drawn to methods for the treatment of any cancer, claims 14-18 are directed to methods for the treatment of a broad variety of cancers and claim 19 is drawn to methods of inhibiting the growth of cancer cells *in vivo*.

Applicants respectfully submit that presently pending claims 1-13 and 14-18 are directed to methods for the treatment of diseases, including cancer, associated with a nonsense mutation and, accordingly, are not drawn to the treatment of any cancer. Applicants take this opportunity to note that the pending claims are indeed tailored to specific types of cancer having a well-defined aetiology, which the compounds of the pending claims have been demonstrated to target.

Applicants note that amended claim 19 is drawn to methods of inhibiting the growth of a cancer cell having a nonsense mutation in its DNA or RNA *in vitro* or *in vivo*, which is also tailored to a specific population of cancer cells.

The Amount of Direction of Guidance Presented

The Examiner acknowledged that the probable mechanism by which the claimed therapeutic method exerts its effect is disclosed and that protocols are provided for the *in vitro* and *in vivo* inhibition of cancer cells. The Examiner stated that the clinically relevant properties such as the toxicity or therapeutic index, are not disclosed.

Applicants respectfully submit that the claims recite the treatment of diseases, including cancer, associated with a nonsense mutation and, accordingly, that the specification

does indeed disclose the mechanism by with the claimed therapeutic methods exert their effects. Furthermore, as the Examiner is aware, an applicant need not provide human clinical data such as toxicity or therapeutic index in order to enable an invention that treats a disorder or disease. *In re Brana*, 51 F.3d at 1566.

The Presence or Absence of Working Examples

The Examiner stated that the specification provides one *in vivo* working example drawn to a specific tumor cell line bearing a p53 nonsense mutation and that *in vitro* examples are give for several p53 nonsense mutation cell lines. The Examiner further stated no working examples are given for tumor cell lines bearing mutations in genes other than p53, or for cell lines in which the oncogenic mutation is a missense or frameshift mutation, and that no examples are give for the treatment of cancers resulting from mutations in genes other than p53.

Preliminarily, Applicants note that the amended claims recite methods directed to diseases associated with nonsense mutations and, accordingly, examples relating to missense or frameshift mutations should not be required.

Applicants respectfully submit that an applicant need not have actually reduced the invention to practice prior to filing and that the presence of an *in vivo* working example and several *in vivo* working examples should weigh heavily towards a finding that the claims are enabled. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). Applicants note that the Federal Circuit specifically addressed this issue and held that *in vivo* and *in vitro* animal models and assays constitute working examples if the art recognizes that they correlate with a specific condition. *See e.g., In re Brana*, 51 F.3d at 1566 (reversing the PTO decision based on a finding that *in vitro* data did not support *in vivo* applications). Applicants respectfully submit that *in vivo* and *in vitro* assays such as those disclosed in the present specification are accepted as correlating with the treatment of the claimed diseases and are what is routinely used by those skilled in the art to determine the utility of candidate compounds. Applicants recognize that all compounds showing promise in a particular animal model or assay will not advance to a clinical study, but such is not a requirement for patentability. *Id.*

Furthermore, the Court of Customs and Patent Appeals has found that claims can be enabled notwithstanding the absence of examples of dosages for human use or animal tests. *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981) (held that applicant's disclosure that novel prostaglandins had certain pharmacological properties and possessed activity similar to known prostaglandins was sufficient to enable one skilled in the art). In explaining its reasoning, the Court stated that the early filing of an application with its disclosure of novel

compounds which possess significant therapeutic use is to be encouraged. *Id.* The Court further stated that specific testing of thousands of compounds...in order to satisfy 35 U.S.C. § 112 would delay disclosure and frustrate, rather than further, the interests of the public and noted that one skilled in the art would know how to use the compounds to determine the specific dosages for the various biological purposes. *Id.*

Thus, Applicants respectfully submit that the working examples provided in the present specification are sufficient to enable the pending claims.

The Quantity of Experimentation Necessary

The Examiner stated that one skilled in the art would have to develop specific therapeutic regimens for each general type of cancer bearing a nonsense p53 mutation and would have to perform further experimentation to develop therapeutic methods for treating cancers not associated with a single nonsense mutation, which would involve optimizing and testing various regimens for each type of cancer. Applicants respectfully submit that Title 35 does not demand the development of such therapeutic regimens or that any human testing occur within the confines of Patent and Trademark Office proceedings. *In re Brana* at 1567 (Testing for the full safety and effectiveness ... is more properly left to the Food and Drug Administration (FDA). This regulatory process is not the same as the enablement requirement under 35 U.S.C. § 112, first paragraph. Using this logic, no pharmaceutical case would be allowed until after FDA approval. Such is not the law.

The Examiner further stated that this process would involve unpredictable experimentation with no guarantee that success is even possible for each case. Applicants respectfully submit that all experimentation is unpredictable and that the correct standard is whether or not the experimentation is undue. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants note that the Federal Circuit has held that a specification is enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989). In addition, Applicants respectfully submit that a guarantee that success is possible is not a requirement for patentability and that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

The Examiner further stated that a patent is not a hunting license, but rather is compensation for the successful conclusion of a search, and that patent protection is not granted for ideas that may or may not be workable. Applicants respectfully submit that the

subject matter of the pending claims is the result of a successful search for compounds having activity as nonsense mutation suppressors, which are useful for treating diseases caused by nonsense mutations. In addition, the data set forth in the present application does indeed show that compounds of the pending claims do work as nonsense mutation suppressor agents.

In view of the above discussion and amendments to the claims more particularly pointing out the types of diseases to be treated (*i.e.*, those associated with a nonsense mutation), Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-19 for lack of enablement should be withdrawn.

II. The Rejection of Claims 1-18 Under 35 U.S.C. § 112, First Paragraph

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse this rejection.

As Applicants understand this rejection, the Examiner's concern is with the use of the term "preventing" in the claims. In particular, the Examiner stated that one would need to know the long-term effectiveness and effects of administration of the compounds of the pending claims, as well as certain aspects of the therapeutic protocols useful for such "preventing."

Applicants respectfully submit that the same arguments set forth above with respect to the *Wands* factors in connection with the "treating" aspect of the pending claims apply to the "preventing" aspect, and note that the pending claims are directed to diseases, including cancer, associated with a nonsense mutation. Applicants further submit that a showing that a drug can be administered over the lifetime of a patient without side effects is not a requirement for patentability. If such were, it would seem to be difficult for an inventor of a therapeutic agent to secure patent protection in his lifetime. Applicants again note that the Federal Circuit has specifically stated that it is the Food and Drug Administration and not the PTO that determines the safety and efficacy of drugs for use in humans. *In re Brana* at 1567 (Testing for the full safety and effectiveness ... is more properly left to the Food and Drug Administration (FDA). Indeed, an applicant need not even demonstrate that an invention is completely safe to satisfy the requirements of 35 U.S.C. § 112. *In re Sichert*, 566 F.2d 1154 (C.C.P.A. 1977) (the Court noted that pharmaceuticals would be more useful if they didn't have any undesirable side effects, but were still useful nonetheless).

Applicants note that a method of "preventing" a disease does not necessarily entail continuous administration of the preventative agent for the remainder of the patient's life, as

the Examiner appears to have interpreted it. Rather, administration could begin when a certain biological marker (*e.g.*, plasma level of protein or mRNA) dictates that prevention is desirable (*e.g.*, prior to the appearance of symptoms) and continue until the biological marker returns to a normal level.

The Examiner further stated that the specification fails to give any rationale as to why the disclosed treatment would be expected to be useful for prevention of disease. Applicants respectfully disagree.

Without being limited by theory, compounds in the pending method of use claims are thought to derive their therapeutic activity from their ability to suppress nonsense mutations. Such nonsense mutations are genetic mutations, and it is well known that those skilled in the art can screen a patient for the presence of such genetic mutations. Accordingly, a patient can be screened by one skilled in the art to determine if the patient possesses such a nonsense mutation and is a candidate for therapy to prevent the disease associated with the mutation. Indeed, Applicants envisioned this type of screening activity as evidenced by the specification as filed at least at page 9, lines 5-11. Thus, contrary to the Examiner's assertion, the term "treating" in the pending method of use claims does not merely denote a hope or a prediction, but is based on knowledge and assays available to those skilled in the art at the time of filing of the present application which allow a patient to be screened to determine if they are a candidate (*i.e.*, "a patient in need thereof") for preventive therapy.

In view of the above discussion and amendments to the claims more particularly pointing out the types of diseases to be treated (*i.e.*, those associated with a nonsense mutation), Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-18 for lack of enablement should be withdrawn.

III. The Rejection of Claim 19 Under 35 U.S.C. § 102(b)

Claim 19 is rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Moss *et al.*, *J. Med. Chem. 31*:786-790 (1988) ("Moss"). In particular, the Examiner has stated that Moss discloses that clitocine is useful for the inhibition of the growth of various leukemia cell lines *in vitro*.

Applicants respectfully note that claim 19 contains the proviso that the cancer cell is not a leukemia cancer cell. Thus, claim 19 does not encompass methods for inhibiting the growth of various leukemia cell lines *in vitro*.

Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. § 102(b) has cannot stand and should be withdrawn.

IV. The Rejection of Claims 1-19 Under 35 U.S.C. § 103(a)

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,324,731 to Kaddurah-Daouk *et al.* ("Kaddurah-Daouk"). In particular, the Examiner has stated that Kaddurah-Daouk discloses methods of inhibiting the growth of tumors resulting from the nonsense mutation of oncogenes such as Rb, DCC, and p53. Applicants respectfully disagree.

At column 3, lines 33-37 pointed to by the Examiner, Kaddurah-Daouk states:

> For instance, loss of anti-oncogene products Rb, DCC or p53 may mimic infection by a DNA tumor virus, leading ultimately to elevated activity of a purine metabolic enzyme(s). These tumors are likely candidates for treatment by the present method.

Contrary to the Examiner's assertion, Kaddurah-Daouk does not teach methods of inhibiting the growth of tumors resulting from the nonsense mutation of certain oncogenes, but rather is directed to inhibition of the growth of cells with elevated activity of at least one purine metabolic enzyme. Kaddurah-Daouk only teaches that tumors which have lost certain anti-oncogenic products are candidates for treatment. Although tumors with a nonsense mutation could fall into the broad class of tumors with a "loss of anti-oncogene products," Kaddurah-Daouk certainly does not teach or suggest the use of any compound to treat or prevent a disease caused by a nonsense mutation.

The focus of Kaddurah-Daouk is inhibiting the growth of cells with elevated activity of at least one purine metabolic enzyme (*see* Kaddurah-Daouk at column 2, lines 17-20). Kaddurah-Daouk discloses that this can be accomplished by either inhibiting the expression of genes encoding for such enzymes or inhibiting the enzymatic activity of the enzymes themselves (*see* Kaddurah-Daouk at column 2, lines 43-48). In other words, the goal of Kaddurah-Daouk is to *inhibit* gene expression or enzymatic activity. The presently claimed methods, to the contrary, are directed to increasing the expression of certain gene products, the absence of which cause disease.

Thus, although Kaddurah-Daouk suggests that the loss of an anti-oncogenic product such as p53 *may* ultimately lead to elevated activity of a purine metabolic enzyme, there is no suggestion or motivation for one of ordinary skill in the art to use clitocine, or any compound, to treat or prevent a disease associated with a nonsense mutation. Kaddurah-Daouk only suggests treating a disease which is associated with elevated activity of a purine metabolic enzyme. In other words, if it was determined that tumor cells from a patient were not characterized by elevated activity of a purine metabolic enzyme, there would be no motivation to administer clitocine, or any compound of Kaddurah-Daouk, regardless of the

level of p53 expression. In addition, there would be no expectation of success with respect to the treatment of such a disease which was not shown to be characterized by elevated activity of a purine metabolic enzyme.

Applicants further submit that with respect to clitocine, Kaddurah-Daouk provides nothing more than a suggestion to try, but does not provide the normally requisite expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In particular, Kaddurah-Daouk itself teaches that of 14 brain creatine kinase (CKB) inhibitors (which are a type of purine metabolic enzyme; *see* Kaddurah-Daouk at column 6, lines 15-17) tested, only four were found to be active (*see* Kaddurah-Daouk at column 27, lines 22-41). Thus, even the fact that a compound is an inhibitor of a purine metabolic enzyme does not provide a reasonable expectation of success with respect to anti-cancer activity. Kaddurah-Daouk merely states that clitocine and its derivatives are inhibitors of adenosine kinase, but does not provide any data with respect to anti-cancer activity which would give one of ordinary skill in the art a reasonable expectation of success with respect to anti-cancer uses of clitocine or related compounds. Rather, Kaddurah-Daouk merely suggests trying clitocine, which is not the proper standard for obviousness. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Thus, Applicants respectfully submit that Kaddurah-Daouk does not provide the normally requisite suggestion or motivation and expectation of success necessary to establish a proper case of *prima facie* obviousness. *In re Vaeck* at 493.

Applicants note that claims 3, 10 and 17 are directed to methods comprising intravenous administration of a compound of formula I, which Kaddurah-Daouk does not teach or suggest with respect to clitocine.

Accordingly, Applicants respectfully submit that the rejection of claims 1-19 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

V. The Provisional Double Patenting Rejection

Claims 1-19 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-10 of co-pending Application No. 11/048,659 (the "'659 application). Per M.P.E.P § 804, a provisional double patenting rejection should continue to be made unless it is the sole remaining rejection in one of the applications. Upon entry of the presently made amendment and remarks, Applicants believe that the sole remaining rejection in the present application will be the provisional double patenting rejection over the '659 application. Accordingly, Applicants respectfully request that the provisional double patenting rejection over the '659 application be withdrawn. Applicants will then consider filing a terminal disclaimer in the '659 application over the present application.

VI. Reference C14

Applicants have noticed that reference C14 was not initialed in the copy of the "List of References Cited by Applicant" enclosed with the Office action mailed June 6, 2006 in connection with the present application. Enclosed herewith is a supplemental "List of References Cited by Applicant" setting forth reference C14. Applicants respectfully request that the Examiner review the document identified on the "List of References Cited by Applicant" as C14, and that the initialed supplemental "List of References Cited by Applicant" be returned to Applicants, indicating the Examiner's consideration of the reference.

Conclusion

Applicants respectfully request that the above remarks be entered in the present application file. No fee is believed to be due in connection with this Response; however, in the event that any fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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